CARDIOVASCULAR MEDICINE

Relation between aortic stiffness and coronary flow reserve in patients with coronary artery disease

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Objectives: To investigate the relation between aortic stiffness and coronary flow reserve (CFR) in patients with coronary artery disease (CAD).
Design: Observational study.
Setting: Coronary care unit of a primary care hospital.
Patients: 192 consecutive patients who underwent coronary angiography.
Main outcome measure: Brachial-ankle pulse wave velocity (ba-PWV), CFR, and severity of CAD.
Results: According to the angiographic findings, patients were divided into four subgroups: patients without significant stenosis (normal coronary artery (NCA) group, n = 28) and those with one vessel disease (1VD group, n = 92), two vessel disease (2VD group, n = 50), or three vessel disease (3VD group, n = 22). ba-PWV increased with the number of diseased vessels and was significantly correlated with the number of diseased vessels (NCA group *v* 1VD group *v* 2VD group *v* 3VD group: 1481 (252) *v* 1505 (278) *v* 1577 (266) *v* 1727 (347) cm/s, $p < 0.001$). CFR had a significant negative correlation with ba-PWV ($r = -0.45$, $p < 0.0001$). The diastolic to systolic velocity ratio obtained in 45 patients also was significantly correlated with ba-PWV ($r = -0.35$, $p < 0.05$). Multiple regression analysis showed that ba-PWV was an independent determinant of CFR ($p < 0.01$).
Conclusions: Coronary flow is altered with aortic stiffening in patients with CAD. These results suggest one possible mechanism for recent reports that aortic stiffness is a key cardiovascular risk factor.

Several studies have suggested that aortic stiffness may predict cardiovascular morbidity or mortality.[1 2] Aortic stiffness has been shown to relate to the degree of epicardial coronary artery disease (CAD) assessed by coronary angiography, although coronary angiography provides information only about the epicardial coronary artery.[3 4]

The objective of this study, therefore, was to investigate the relation between aortic stiffness and the coronary circulation. In this study, we measured brachial-ankle pulse wave velocity (ba-PWV) as a known marker of aortic stiffness.[5 6] We compared these measurements with the results of coronary angiography and flow velocity measured with a coronary Doppler guidewire.

METHODS

Patient enrolment

Our patient population comprised 192 consecutive patients who were admitted to the Osaka City University Hospital to be examined for CAD. We excluded patients: (1) with an ankle to brachial blood pressure (BP) ratio < 0.9; (2) with atrial fibrillation or flutter; (3) with valvar disease, cardiomyopathy, or congenital heart disease; (4) with acute coronary syndrome; (5) who had undergone coronary artery bypass graft surgery; and (6) with end stage renal disease who were on haemodialysis.

Pulse wave velocity measurements

All patients underwent ba-PWV measurement as a marker of aortic stiffness before coronary angiography. ba-PWV was measured with an automatic waveform analyser (form PWV/ABI, Colin, Komaki, Japan) as previously reported.[7–9] In this study, the average of right and left ba-PWV was used for analysis.

Coronary angiography

Coronary angiography was performed by a standard technique.[10] All patients initially received a bolus injection of 3000 IU of heparin and intracoronary isosorbide dinitrate (2 mg) before angiography. Two independent observers blinded to the results of the ba-PWV measurements reviewed the coronary angiograms separately. Stenosis $> 75\%$ detected angiographically in the major coronary vessel was defined as significant stenosis. The number of diseased vessels was determined from the number of major coronary arteries with significant stenosis or with a history of any intervention.

Intracoronary blood flow velocity measurements

Coronary flow velocity was measured in 79 patients with $< 25\%$ diameter stenosis, stenosis length < 10 mm, and no collateral flow as confirmed by angiography. In this study, we did not measure flow velocity in a coronary artery with a history of myocardial infarction or prior intervention. After completion of diagnostic coronary angiography, we measured coronary flow velocity with a 0.014 inch coronary Doppler guidewire as we previously described.[11] In this study, 30 μg of intracoronary adenosine triphosphate was administered over 10 seconds to obtain maximum hyperaemia. Diastolic to systolic velocity ratio (DSVR) (time averaged diastolic peak velocity divided by time averaged systolic peak velocity) was also calculated. DSVR in the right coronary artery was excluded because of its specific perfusion character.[12]

Abbreviations: 1VD, one vessel disease; 2VD, two vessel disease; 3VD, three vessel disease; ba-PWV, brachial-ankle pulse wave velocity; BP, blood pressure; CAD, coronary artery disease; CFR, coronary flow reserve; DSVR, diastolic to systolic velocity ratio; NCA, normal coronary artery

Statistical analysis

Values are expressed as mean (SD). Categorical data were compared by χ^2 analysis or Fisher's exact test. Analysis of variance with Bonferroni/Dunn correction was used to test for differences in continuous variables between groups. Correlation between the number of diseased vessels and ba-PWV or number of coronary risk factors was assessed by Spearman's correlation coefficient by rank. Multiple regression analysis was performed for several parameters, predicting ba-PWV and coronary flow reserve (CFR). We examined the sensitivity and specificity of ba-PWV for CFR by using receiver operating characteristic curves. A value of $p < 0.05$ was considered significant.

RESULTS

Clinical backgrounds of patients

A total of 192 patients (165 men, 62.1 (9.2) years old) were enrolled in this study. ba-PWV was successfully measured in all. From the results of coronary angiography, patients were divided into four subgroups: patients without significant stenosis (normal coronary artery (NCA) group, n = 28) and patients with one vessel disease (1VD group, n = 92), two vessel disease (2VD group, n = 50), and three vessel disease (3VD group, n = 22). Table 1 summarises the patients' characteristics.

The four groups did not differ significantly in sex and age. However, incidence of hypertension and diabetes mellitus tended to increase with the number of diseased vessels. The number of coronary risk factors also increased with the number of diseased vessels (NCA *v* 1VD *v* 2VD *v* 3VD: 2.1 (1.2) *v* 2.3 (1.0) *v* 2.7 (1.2) *v* 3.0 (1.3), $p < 0.001$).

Aortic stiffness and epicardial coronary artery stenosis

Systolic BP was significantly higher in patients in the 3VD group than in patients in both the NCA group ($p < 0.05$) and the 1VD group ($p < 0.05$). Diastolic BP was significantly lower in the 3VD group than in the NCA group ($p < 0.05$) and the 1VD group ($p < 0.05$). Patients in the 3VD group had significantly higher pulse pressure than patients in the NCA group ($p < 0.05$) and the 1VD group ($p < 0.01$) as table 1 and fig 1A–C show. Similarly, patients in the 3VD group had significantly higher ba-PWV than patients in the NCA group ($p < 0.01$), the 1VD group ($p < 0.01$), and the 2VD group ($p < 0.05$) as table 1 and fig 1D show. Furthermore, ba-PWV was significantly correlated with the number of diseased vessels ($p < 0.001$). Multiple regression analysis was performed for several parameters (male sex, age, and coronary risk factors) to predict ba-PWV. This model indicated that ba-PWV was independently correlated with age ($p < 0.0001$), hypertension ($p < 0.01$), and diabetes mellitus ($p < 0.01$).

Aortic stiffness and coronary microcirculation

In this study, CFR was obtained in 79 patients (25 in the NCA group, 37 in the 1VD group, and 17 in the 2VD group). CFR of the 2VD group (2.6 (0.4)) was significantly lower than that of the NCA group (3.3 (0.8, $p < 0.01$) and 1VD group (3.1 (0.7), $p < 0.01$). Of the 79 patients, 45 had flow velocity measured in the left coronary artery and were therefore eligible for DSVR measurement. Thirty four patients were excluded from DSVR measurement (in 24 patients flow velocity was measured in right coronary artery and in 10 patients we were unable to obtain satisfactory wave patterns). The results of DSVR measurements was follows: NCA group: 2.0 (0.3); 1VD group: 1.7 (0.3); and 2VD group: 1.73 (0.3) ($p < 0.05$). Both CFR and DSVR were significantly correlated with ba-PWV (CFR: $r = -0.45$, $p < 0.0001$; and DSVR: $r = -0.35$, $p < 0.05$) as fig 2 shows. In univariate analysis, CFR also correlated significantly with age and DSVR correlated significantly with systolic BP. However, there was no significant correlation between DSVR and CFR. Furthermore, we performed multiple regression analysis to predict CFR. Age, male sex, coronary risk factors, systolic and diastolic BP, the number of diseased vessels, and ba-PWV were the independent variables. This model showed that ba-PWV was an independent determinant of CFR (standard regression coefficient -0.44, $p < 0.01$). From the receiver operating characteristic curve, the value of ba-PWV > 1600 cm/s provided the best combination with a sensitivity 75% and a specificity of 76.1%.

DISCUSSION

In this study, we showed that aortic stiffness relates not only to epicardial coronary artery stenosis but also to impaired coronary microcirculation. Atherosclerosis of the aorta and coronary artery is reported to develop in parallel.[13] However, to our knowledge, very few studies have investigated the relation between aortic stiffness and the coronary microcirculation in humans.[14–16]

Aortic stiffness and coronary microcirculation

Atherosclerotic changes in the epicardial coronary artery has a central role in the pathogenesis of CAD, so early detection of atherosclerotic change is of great importance. However, conventional angiography provides only a silhouette of the vascular lumen, so it is difficult to assess the early stage of atherosclerosis by this method alone. One approach is to

Table 1 Clinical background of patients

	NCA (n = 28)	1VD (n = 92)	2VD (n = 50)	3VD (n = 22)	p Value
Age (years)	62.0 (9.4)	61.1 (9.5)	63.2 (8.0)	64.0 (10.2)	0.44
Men	22 (79%)	80 (87%)	44 (88%)	19 (86%)	0.68
Coronary risk factors					
Hypertension	12 (43%)	48 (52%)	30 (60%)	18 (82%)	0.03
Diabetes mellitus	5 (18%)	23 (25%)	21 (42%)	10 (45%)	0.03
Hypercholesterolaemia*	12 (43%)	46 (50%)	25 (50%)	11 (50%)	0.92
Smoking	15 (54%)	44 (48%)	26 (52%)	13 (59%)	0.79
Family history of CAD	8 (29%)	15 (16%)	18 (35%)	5 (23%)	0.07
Obesity (BMI >25 kg/m^2)	6 (21%)	33 (36%)	14 (28%)	10 (45%)	0.25
Systolic blood pressure (mm Hg)	123.2 (11.5)	121.9 (15.6)	124.2 (17.3)	125.9 (13.0)	0.03
Diastolic blood pressure (mm Hg)	76.0 (7.3)	75.0 (8.8)	72.4 (8.1)	71.9 (7.2)	0.03
Pulse pressure (mm Hg)	48.0 (8.0)	47.2 (11.0)	48.8 (11.7)	54.9 (11.2)	0.04
Pulse wave velocity (cm/s)	1481 (252)	1505 (278)	1577 (266)	1727 (347)	0.02

Data are presented as mean (SD) or number (%).
*>5.7 mmol/l.
1VD, one vessel disease; 2VD, two vessel disease; 3VD, three vessel disease; BMI, body mass index; CAD, coronary artery disease; NCA, normal coronary artery.

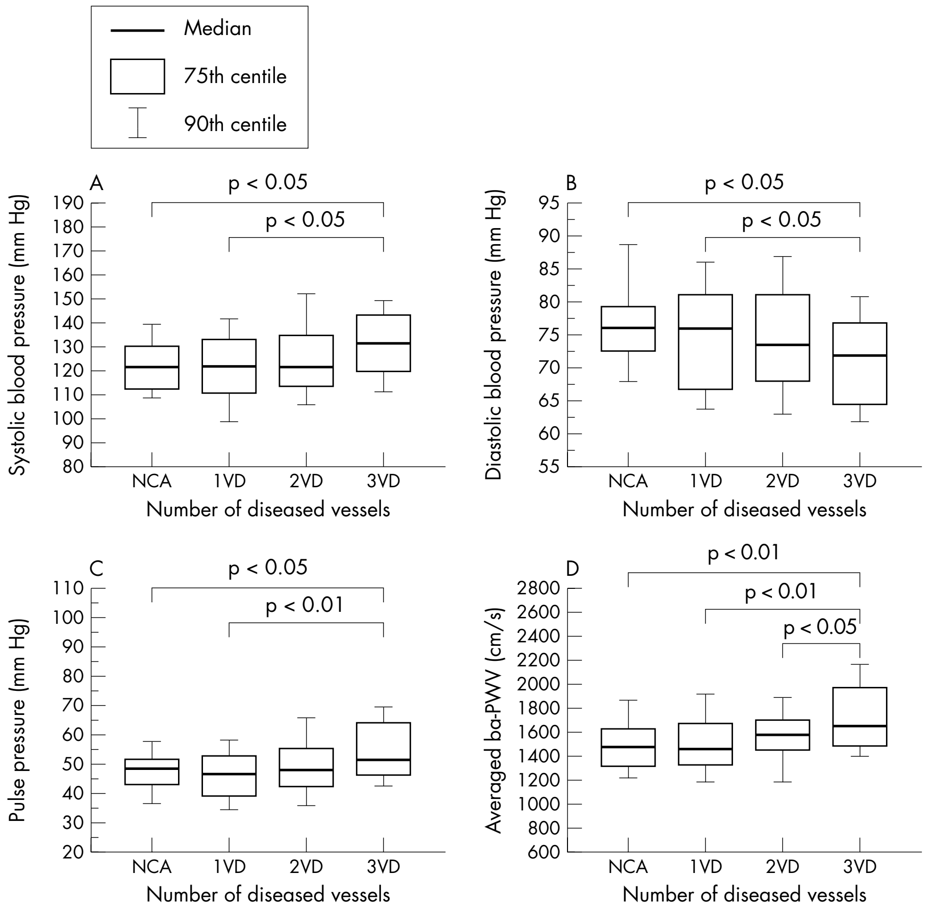

Figure 1 Relation between the number of diseased vessels and aortic stiffness. In the four groups, patients in the group with three vessel disease (3VD) had significantly (A) higher systolic blood pressure and (B) lower diastolic blood pressure than patients in the groups with normal coronary arteries (NCA) and one vessel disease (1VD) (each $p < 0.05$). (C) Patients in the 3VD group also had significantly higher pulse pressure than patients in the NCA group ($p < 0.05$) and the 1VD group ($p < 0.01$). (D) Patients in the 3VD group had significantly higher pulse wave velocity (PWV) than patients in the NCA group and the 1VD group (each $p < 0.01$) and the group with two vessel disease (2VD) ($p < 0.05$). Brachial-ankle PWV (ba-PWV) was significantly correlated with the number of diseased vessels ($p < 0.001$).

monitor CFR, since a decrease in CFR is reported to precede epicardial coronary artery stenosis progression.[17–19] Adenosine induced CFR is thought to represent, at least in part, endothelial function.[20 21] Previously, Nemes *et al*[15] investigated the relation between CFR and aortic stiffness obtained by transoesophageal echocardiography in patients with CAD, although it is thought to be rather invasive. So use of ba-PWV as a marker of aortic stiffness may well be one useful non-invasive method of assessing coronary artery endothelial function in patients with CAD.

Our results of multiple regression analysis showed that ba-PWV was an independent determinant of CFR. In this model, however, age did not come out as a significant predictor of CFR. This may be because of the small number of patients and the strong relation between age and pulse wave velocity. As described in several papers, CFR as well as aortic stiffness was reported to be impaired by several coronary risk factors.[17 18 22–26] Therefore, it may be difficult to ascertain whether aortic stiffness has a clear cut causative role in inducing the observed impairment of CFR. Meanwhile, several studies investigating the relation between aortic stiffness and coronary circulation suggest a potential role of aortic stiffness in the reduction of coronary circulation. Aortic stiffening leads to left ventricular hypertrophy and altered coronary perfusion. Indeed, left ventricular hypertrophy may impair CFR through the increase of microvessel resistance in

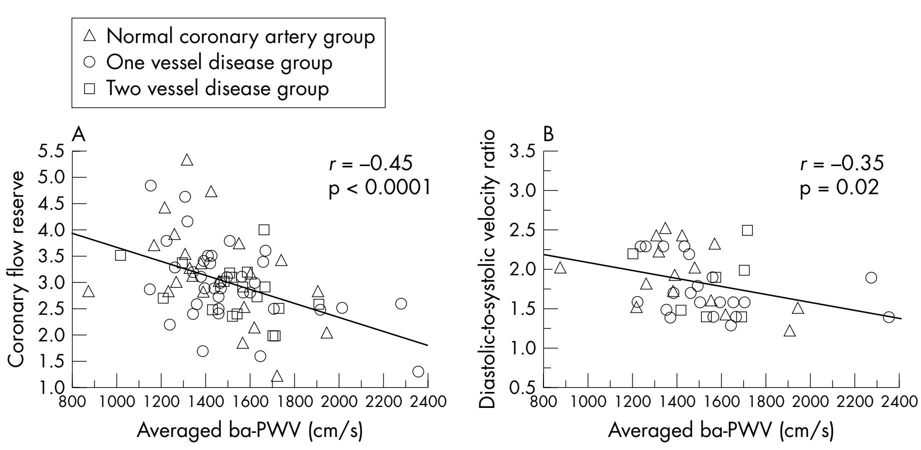

Figure 2 (A) Coronary flow reserve had a significant negative correlation with ba-PWV ($r = -0.45$, $p < 0.0001$). (B) Diastolic to systolic velocity ratio had a significant negative correlation with ba-PWV ($r = -0.35$, $p < 0.05$).

the coronary bed.[27] Furthermore, aortic stiffness has been reported to decrease coronary flow and to have additive effects on myocardial ischaemia.[28 29] Saeki *et al*[30] and Kass *et al*[31] have reported that basal myocardial flow can actually be enhanced in an experimental bypass model of aortic stiffening, even at matched work loads, primarily due to augmentation of coronary flow during systole. Their results may support our findings that aortic stiffness had a weak negative correlation with DSVR and that CFR did not correlate with DSVR. Indeed, Kingwell *et al*[32] have recently reported that aortic stiffness is a predictor of the ischaemic threshold of patients with CAD. The alteration of coronary flow, as we showed in our study, is one possible mechanism that explains their results.

Aortic stiffness is now held to be one of the most important cardiovascular risk factors, and several recent studies have indeed shown that aortic stiffness is predictive of vascular morbidity or mortality.[1 2] Our own results suggest that both epicardial coronary artery stenosis and microcirculatory dysfunction are possible mechanisms of aortic stiffness correlated with cardiovascular events in humans.

Limitations

Our study may be said to have several limitations. Firstly, measuring pulse wave velocity is methodologically limited. We assessed vessel path length by an equation, although unfolding of the aorta with increasing age may make such an approximation less reliable. Secondly, the coronary microcirculation was assessed only in coronary arteries without significant stenosis—namely, patients with 3VD were excluded. Thus, our results may not be applicable to all patients with CAD. Furthermore, we did not perform intravascular ultrasound analysis. Atheromatous plaque in the artery without angiographically significant stenosis possibly reduced coronary flow. Thirdly, in this study, we used only one dose of adenosine (30 μg) to obtain CFR. Our dose might not have been sufficient to obtain maximum hyperaemia. Lastly, our patient population was small, and a large scale study is required to confirm the validity of our results.

Conclusion

In this study, we showed that CFR and DSVR decrease in concert with increased aortic stiffness. This is one of the first studies showing that aortic stiffness is an independent predictor of coronary microcirculation dysfunction in patients with CAD. We think that measurement of ba-PWV may well be one useful non-invasive method of assessing coronary artery endothelial function. Also, our results may be one mechanism explaining recent reports that aortic stiffness is an important cardiovascular risk factor.

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